Joint MPH Program

University of Gondar and Addis Continental Institute of Public Health

Determinant Factors and Time To Sputum Smear And Culture Conversion Among Multidrug Resistant Tuberculosis Patients in St. Peter's Tuberculosis Specialized Hospital, Addis Ababa

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A Thesis submitted to the School of Graduate Studies of University of Gondar in Partial Fulfillment of the Requirements for the Degree

Of Masters in Public Health

May 5, 2011

Addis Ababa

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ACRONYMS

ACIPH	Addis Continental Institute of Public Health
AFB	Acid Fast Bacilli
AHRI	Armauer Hansen Research Institute
AIDS	Acquired Immune Deficiency Syndrome
Am	Amicacin
Cm	Capriomycin
Cs	Cyclocerin
DM	Diabetes Mellitus
DOTS	Directly Observed Treatment Short Course
DST	Drug Sensitivity Test
ETM	Ethambutol
Eto	Ethionamid
EHNRI	Ethiopian Health and Nutrition Institute
EPI INFO	Epidemiology Information
FMOH	Federal Ministry of Health
G.C	Gregorian calendar
HIV	Human Immune Deficiency Virus
INH	Isoniazid
IRB	Institutional Review Board
Km	Kanamycin
Lfx	Levofloxacin
Mfx	Moxifloxacin
MDR	Multi Drug Resistant
M.TB	Mycobacterium Tuberculosis
NRL	National Reference Laboratory
OPD	Out Patient Department
PASS	Para Amino Salicylic Acid
P-TB	Pulmonary Tuberculosis
Z	Pyrazinamid
RIF	Rifampicin
STM	Streptomycin
SPSS	Statistical Package for Social Science
TB	Tuberculosis
UoG	University of Gondar
WHO	World Health Organization
X-DR	Extensively Drug Resistant

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ABSTRACT

BACKGROUND: MDR-TB is increasing and now it has become a big threat to the National tuberculosis program. The Ethiopian government has identified MDR-TB as one of the priority public health problems and it is committed to initiate comprehensive treatment of MDR cases in the country. With the approval of the Green Light committee, it has started the treatment of MDR-TB since February 2009 by selecting a pilot project which is at the St. Peter's TB Specialized hospital in Addis Ababa and rapid expansion to the regions is foreseen and preparation is underway. In this study we will assess the time to sputum smear and culture conversion.

OBJECTIVE: To assess the time to sputum smear and culture conversion and determinant factors associated with conversion among MDR-TB patients admitted to St. Peter's TB-specialized hospital.

METHOD: Retrospective Cross sectional study among MDR-TB patients admitted to St. Peter's TB-specialized hospital starting from February 2009. A total of 149 patients who fulfill the inclusion criteria are included in the study. Data were collected using compilation form from the available medical records, treatment charts, bacteriologic reports and chest x-ray results.

RESULTS: Sputum smear conversion was found to be 107(71.81%), 133(89.26%) in the first and second month respectively. Age was found to be significantly associated with sputum conversion P: 0.032, and 0.027. The Culture conversion in the second month revealed 73(48.99%). HIV status, presence of pleural effusion were factors found to be associated with culture conversion at 2 months, HIV positives and those with pleural effusion being late converters. Culture conversion in the third month revealed 123(82.55%) and here those age group ≤ 24 and HIV negatives were found to covert early

CONCLUSION AND RECOMMENDATION This study revealed that with strict in-patient treatment, of nearly 80% of sputum smear and culture conversion could be achieved. This can reduce the length of in-patient stay (which at present is extending up to six months) and more patients can get chance for MDR-TB treatment. The younger age group ≤24 years, HIV negatives and those with no pleural effusion are the early converters therefore minimizing the length of stay in the hospital to 3 months can be considered on these patients.

INTRODUCTION: Tuberculosis (TB) is a major public health problem and has been recognized throughout the world since early ages. Since 1950 control efforts have been initiated by establishment of sanatoria and later strengthening by implementation of DOTS strategy in the early 1990's. Poverty, homelessness, congregate settings, alcoholism, drug abuse and HIV are the main risk factors for TB. At present tuberculosis control strategy in Ethiopia relies on WHO recommended stop-TB strategy and it has been implemented since 2006. (1)

The directly observed treatment short course (DOTS) strategy has important components: government commitment to ensure sustained and comprehensive TB control activities; case detection by sputum smear microscopy among symptomatic patients; standardized short course chemotherapy using regimens six to eight months; regular un-interrupted supply of all essential anti-TB drugs and laboratory supplies; and standardized recording and reporting system. (2; 3; 4)

The current threats for DOTS strategy in Ethiopia are; the detection rate remains low, at 36%, compared with World Health Organization's target of 70% detection. The number of TB cases is likely to increase as Ethiopia's Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) epidemic expands. Self withdrawal from treatment, the worsening socio-economic trends are factors for the increase of TB incidence. Following all these the other main threat is the emergence of Multi-drug Resistant Tuberculosis (MDR-TB) and also Extensively Drug- Resistant Tuberculosis (X-DR TB). (5)

Multi-drug Resistant Tuberculosis (MDR-TB) is defined as resistance to Ionized (INH) and Rifampicin (RIF), the two most important first line anti-TB drugs. MDR-TB is a man-made problem. When patients stop taking or do not take enough of the right medications, the poor quality of anti-tuberculosis drugs supply and due to the poor follow-up of the means of tuberculosis transmission leads to the emergence and spread of mycobacterium tuberculosis strains resistant to multiple drugs which represent a major public health problem in a number of countries and an obstacle to effective global TB control. In addition, new cases of extensively drug resistant tuberculosis(X-DR) are also emerging which makes the condition even worst.

X-DR is defined as resistance to a floroquinolone and at least one second line injectable drug Kanamycin (Km), Amicacin (Am), Capreomycin (Cm), Streptomycin (Stm) in addition to INH and RIF resistance. (6); (7); (1). MDR-TB is a growing problem in resource-poor settings where adequate diagnosis and treatment are often unavailable. Sub-Saharan Africa would seem to have all of the conditions for a "perfect-storm" of HIV infection and MDR-TB. (8)

The Ethiopian government has identified MDR-TB as one of the priority public health problems and is committed to initiate comprehensive treatment of MDR-TB cases in the country. Therefore, the programmatic management of MDR-TB in Ethiopia is introduced in a step-wise manner, starting from a Green Light Committee approved pilot project program in Ababa (St. Peter's Tb specialized hospital) and rapid expansion to the regions is foreseen and preparation is underway. St. Peter's Tb specialized hospital, has started treating MDR-TB cases starting from February 2009. The site was selected as a pilot project for many reasons: It has a long history of TB management; at present it is the only federal hospital specialized in TB care which has given the staff ample experience in TB management; the setting is spacious enough to accommodate renovation and building of new structures. The staff has also taken the initiative to treat some patients with MDR-medication imported privately. It also has a good collaborative partnership with the Ethiopian Health and Nutrition Research Institute (EHNRI) housing the National Reference Laboratory (NRL). (1) During the treatment period, the MDR-TB patients are being followed as in-patient till two consecutive culture results are reported negative. When they reach that point in time, they are then discharged to follow the treatment at OPD level. All doses are directly observed. (1) In this study we would like to assess the time it takes for a patient to convert to a negative-sputum smear and negative culture result and the determinant factors associated with conversion. This will have an impact on the duration of admission of MDR-patient, which at present extends from three to six months. Since we are expecting that we can obtain early conversion, it is anticipated that this will help in reducing the hospital stay of the patients and will increase the turnover. This will enable us to give chance to a larger number of MDR-patients to be treated. There-by we can inform policy makers and guideline developers on the optimal time of MDR patient stay in the hospital so that they may decide to allocate the necessary resources accordingly.

LITRATURE REVIEW

TB EPIDEMIOLOGY (Global and local)

Tuberculosis is a preventable and curable disease, but remains as the biggest public health problem and a leading cause of morbidity and mortality in the world. One third of the world's population is estimated to be infected with tubercle bacilli and hence at risk of developing active disease. Globally, in 2008, the annual incidence of TB, expressed as the number of new TB cases was about 8.9-9.9 million people (7.4 million of these in Asia and Sub-Saharan Africa), the annual number of deaths due to TB among HIV negative people was 1.1-1.7 million and 0.45-0.62 million TB deaths among HIV positive people. In developing countries, TB comprises 25% of all avoidable adult deaths. It is estimated that nearly one million (11%) of the total TB cases are children less than 15 years of age. TB is killing nearly 5000 people every day (2-3million/yr). The number of notified cases of TB in 2008 was 5.7 million, equivalent to 55-67% of all incident cases. (9) ;(10); (1)

Ethiopia is ranking seventh among the world's 22 high-burden countries responsible for 80% of the world's TB burden. Ethiopia had an estimate of 314,267 TB cases, with incidence rate of 378 cases per 100,000 populations in the year 2007. (11); (12)

TB Control Strategies: The components of DOTS strategy are: government commitment to ensure sustained and comprehensive TB control activities; case detection by sputum smear microscopy among symptomatic patients self reporting to health facilities; standardized short course chemotherapy using regimens six to eight months; regular, uninterrupted supply of all essential anti-tuberculosis drugs and laboratory supplies; and standardized recording and reporting system.(1); (2); (4)

In MDR-TB, the components of DOTS strategy are: sustained political commitment; appropriate case-finding strategy including quality-assured culture and drug susceptibility testing (DST); appropriate treatment strategies that use second line drugs under proper case management conditions; uninterrupted supply quality-assured second-line anti-tuberculosis drugs; recording

and reporting system designed for drug resistance-TB control programs that enables performance monitoring and evaluation of treatment outcomes. (1)

Global and Local status of MDR-TB: The emergence of resistant to anti-tuberculosis drugs, and particularly of multi-drug-resistant TB (MDR-TB), has become a major public health problem in a number of countries and an obstacle to effective global TB-control. Nearly half a million cases of MDR-TB emerge every year as a result of under-investment in basic activities to control TB, poor management of supply and quality of anti-tuberculosis drugs, improper treatment of TB patients and poor control of the transmission of the disease in congregate settings. MDR-TB can be treated and cured but treatment regimens are complicated, lengthy and expensive. Medications that are currently available can produce crippling side effects and are less effective than drugs for non-resistant TB. If left untreated, however MDR-TB not only kills the patient but can spread to other people, where it may develop additional drug resistance. In many areas such as Africa the extent of drug-resistant is unknown and in most resource-constrained countries the treatment of patients with MDR-TB is absent or inadequate. MDR-TB is defined as resistant to INH and RIF, the two most important first-line anti-tuberculosis drugs. The worst was yet to come: in 2006, extensively drug resistant TB (XDR-TB) emerged. This is defined as resistant to first and second line drugs. This is a very serious emerging threat to global public health. (1, 6, 8)

According to WHO 2008 report, in Ethiopia, 5825 MDR-TB cases (4964 among newly diagnosed and 861 among previously treated TB cases) were estimated to have occurred in 2006. According to the anti-TB drug resistance survey conducted nationwide in 2005 (EHNRI/FMOH), among 804 newly diagnosed TB cases 1.6% were found to be infected with MDR-TB. The rate of MDR TB among specimens from 76 previously treated TB cases was 11.8%. The same survey reported that, TB with Isoniazid mono-resistance and Rifampicin mono-resistance, among new TB cases, was 2% and 1%, respectively. Notified prevalence of mono-resistance to INH and Rifampicin among previously treated TB cases was 5.3% and 1.3%, respectively. (1)

Resistance to anti-tuberculosis drugs has now become a threat to national tuberculosis program in both developed and developing countries. MDR-TB may be responsible for prolonged shedding of bacilli. The treatment for MDR-TB is more expensive, toxic and difficult to

administer. Therefore, the importance of patient and health care staff compliance, case finding and resistance surveillance has to be stressed. The cost for treatment of the increasing MDR-TB will be a greater financial burden on the already over stretched budgets of national, international and non-governmental organizations. (3)

Treatment of MDR-TB:

For treatment of multidrug-resistant TB or TB with an isolate resistant to at least isoniazid and rifampicin, the status of Mycobacterium cultures is generally used to guide therapy for patients treated in either resource-limited or resource replete settings and is considered the most important interim indicator of the efficacy of treatment for multidrug-resistant TB. (13); (14)

Treatment of patients with multidrug-resistant TB is on the basis of results of drug susceptibility testing (DST) obtained before the treatment initiation. Each dose is given as directly observed therapy (DOT) throughout the treatment. The duration of MDR-TB treatment is 18 to 24 months. The intensive phase being a minimum of six months and the continuation phase 12 to 18 months. Patients with MDR-TB confirmation but not with full DST result are treated with Ethambutol, Pyrazinamid (Z), Kanamycin (Amicacin), Levofloxain (Lfx), Ethionamid (Eto) & Cycloserin (Cs). MDR-TB patients susceptible to both Kanamycin and Quinolons are treated as in the first case. MDR-TB patients susceptible to Kanamycin but resistant to Quinolons are treated with Ethambutol, Pyrazinamid, Kanamycin/(Amicacin), Moxifloxacin, Ethionamid, Cycloserin & Para Amino Salicylic Acid (PAS). Extensively drug resistant tuberculosis cases, that is MDR-TB and resistant to Quinolons and Kanamycin are treated with Ethambutol, Pyrazinamid, Capreomycin, Moxifloxacin (Mfx), Ethionamid, Cycloserin & PAS. (6)

The increasing worldwide incidence of extensively drug resistant tuberculosis (XDR-TB) has emerged as a threat to public health and tuberculosis control. Treatment outcomes have varied among studies, and data on long-term survival are still scarce. In a cohort retrospective study conducted in South Korea, medical records were reviewed of patients newly diagnosed with or retreated for MDR-TB from 2000 to 2002. The study was monitored for 3 to 7 years after the initiation of treatment. Initial treatment outcome and cumulative survival rates were analyzed and predictors of treatment success and survival were defined. Of 1407 patients with MDR-TB

75 (5.3%) had XDR-TB at treatment initiation. The default rate was high (453/1407; 32%) and patients with XDR-TB had lower treatment success (29.3 vs. 46.2%; P=0.004) and higher all cause (49.3 vs.19.4%; P<0.001) and TB related disease mortality (41.3 vs.11.8%; P<0.001) than other patients with MDR-TB. The presence of XDR-TB significantly affected treatment success (odds ratio, 0.23; 95% confidence interval, 0.08-0.64; P=0.005), all cause mortality (hazards ratio, 3.25; 95% CI, 1.91-5.53; p< 0.001), and TB related mortality (hazards ratio, 4.45; 95% CI, 2.48-8.00; P<0.001) on multivariate analyses. The study concluded that XDR-TB occurred in a substantial proportion of patients with MDR-TB, and was the strongest predictor of treatment outcomes and long-term survival in patients with MDR-TB. Adequate TB control policies should be implemented to prevent the further development and spread of drug resistance. (15); (16); (17)

A retrospective cohort study done in Latvia among civilian patients with multidrug resistant TB treated with the DOTS-plus strategy between 1 January and 31 January 2000 showed that among 167 patients who were sputum culture-positive at initiation of second-line therapy, 129 (77%) converted in a median time of 60 days (range, 4 to 462 days) and 38 (23%) did not convert. Independent predictors of a longer sputum culture conversion time included previous treatment for multi-drug resistant TB, high initial sputum culture colony count, bilateral cavitations on chest radiography, and the number of drugs the initial isolate was resistant to at treatment initiation. Treatment outcomes were statistically significantly worse for patients who did not convert their sputum culture within 2 months. (18)

Little is known about treatment of multi-drug resistant tuberculosis (MDR-TB) in high HIV-prevalence settings such as Sub-Saharan Africa. A retrospective analysis of early outcomes of the first cohort of patients registered in the Lesotho national MDR-TB program was done between July 21, 2007 and April 21, 2008. Seventy-six patients were included for analysis. Patient follow-up ended when an outcome was recorded, or on October 21, 2008 for those still on treatment. Fifty-six patients (74%) were infected with HIV; the median CD4 cell count was 184 cells/μl (range 5–824 cells/μl). By the end of the follow-up period, study patients had been followed for a median of 252 days (range 12–451 days). Twenty-two patients (29%) had died,

and 52 patients (68%) were alive and in treatment. In patients who did not die, culture conversion was documented in 52/54 patients (96%). One patient had defaulted, and one patient had transferred out. Death occurred after a median of 66 days in treatment (range 12–374 days). The study concluded that in a region where clinicians and program managers are increasingly confronted by drug-resistant tuberculosis, this report provides sobering evidence of the difficulty of MDR-TB treatment in high HIV-prevalence settings, and further research is urgently needed to improve MDR-TB treatment outcomes in high HIV-prevalence settings. (19)

Although type 2 diabetes (DM) is a recognized risk factor for development of tuberculosis (TB), impact on treatment is unclear. Using retrospective survival analysis done in south Texas, between 1996 and 2002 on 469 culture-positive TB patients identified that Diabetes to be an independent risk factor for a 5-day delay in mycobacterium clearance within the first 60 days of treatment. The association of diabetes with tuberculosis is a re-emerging problem because of the rapid rise worldwide of type 2 diabetes. (20) ;(21)

For patients with drug susceptible –TB, treated in resource limited settings, diagnosis is based on the presence of acid-fast bacilli identified in sputum through evaluation with smear microscopy. Patient management, including duration of treatment and final treatment success, is based on conversion of sputum smears to acid-fast bacilli-negative status. (22)

Conversion of sputum Mycobacterium cultures from positive growth to negative growth of Mycobacterium tuberculosis in patients with pulmonary tuberculosis (PTB) is considered the most important interim indicator of the efficacy of anti-TB pharmacologic treatment for multidrug-resistant disease. (18)

Rational of the Study: The Ethiopian government has identified MDR-TB as one of the priority public health problems and it is committed to initiate comprehensive treatment of MDR-TB cases in the country. The pilot program in Addis Ababa (St. Peter TB specialized hospital) started two years back (February 2009) for the first time in the country after the approval of the Green Light Committee. Rapid expansion to the regions is foreseen and preparation is underway. Thus, in Ethiopia, at this point in time there is nothing to say regarding the MDR-TB treatment outcome. (1)

In this study we would like to assess the time it takes for a patient to convert to a negative sputum smear and sputum culture results and the determinant factors associated with conversion. This will help us to identify how early are MDR-TB patients having their sputum smear and culture conversion, which in-turn will determine the duration of hospital stay of the patients. Now the hospital stay is extending 3-6 months; which after this research is anticipated to be minimized only to three or even less months. Therefore, we can inform policy makers and guide line developers on the optimal time of MDR patient stay in the hospital so that they may decide to allocate necessary resources accordingly.

OBJECTIVE

General objective:

To assess the time of smear and culture conversion and determine factors affecting conversion among MDR P.TB patients admitted to St. Peter TB specialized hospital Addis Ababa, Ethiopia.

Specific objective:

- To determine the time to sputum smear conversion
- To determine the time to sputum culture conversion
- To identify the determinant factors associated with sputum smear culture conversion

METHODOLOGY

Study Design; is Retrospective Cross sectional study.

Study Area:

The study area is St. Peter's TB Specialized hospital. It is located in Gulele Sub-city, wereda 01, Addis Ababa. It was established in 1963 G.C. At that time, it was called TB Demonstration and Training Centre or Sanatorium. The out-patient and the in-patient departments had separate administrative bodies and two different campuses for a long period of time. The administrative bodies joined together few years back and the two campuses were brought together since the beginning of September, 2010.

St. Peter's TB specialized hospital is the only referral hospital in the country for pulmonary tuberculosis cases. Most of the patients that are served by the hospital are those who are critically ill, those coming from the most rural areas and those who are poor and do not have any support.

At present the hospital has 218 administrative staff and 161 technical staff. Currently, more than 32,997 patients are being served every year. The main activities of the hospital include clinical services, diagnostic services and research activities. Since February 2009, the hospital has started treating MDR-TB patients as a first pilot project in Ethiopia. In the future, the hospital will serve as a national MDR-TB referral centre in case of severe side effects and as a centre of excellence and training during the scaling up of MDR-TB treatment to the regions.

Source population:

The source populations are all Multi-Drug Resistant Tuberculosis patients.

Study population:

All Multi-Drug Resistant Tuberculosis patients admitted and treated with second-line anti-tuberculosis treatment in St. Peter's TB-specialized hospital.

Sample size

The required sample size for the study is determined using single population proportion method. Thus we used the formula: $n = Z \frac{\alpha}{2}^2 * P \frac{(1-P)}{d^2}$

- n = sample size
- $Z \frac{\alpha}{2}^2$ = Z-score at 95% confidence interval = 1.96
- P = Smear/Culture conversion rate at third month (0.88 from literature and with observation)
- d = margin of error (0.05)

$(1.96)*(1.96)* \frac{(.88)*(0.12)}{(0.05)*(0.05)}$ = 163 is the sample size

Sampling technique

In St. Peter's TB Specialized hospital there were 160 Multi-drug resistant patients who were under treatment with second line Anti-TB drugs. All patients with all information needed for the study were included.

Inclusion Criteria

All patients admitted and treated for MDR-TB at St. Peter's TB-Specialized Hospital

Exclusion Criteria

Patients whose charts were not complete with all information needed for the study were excluded.

Operational Definitions

- Tuberculosis: (TB) is a bacterial disease caused by Mycobacterium tuberculosis (occasionally by Mycobacterium bovis and Mycobacterium africanum).
- Multi-Drug Resistant Tuberculosis: (MDR-TB) is TB that is resistant at least to Isoniazid (INH) and rifampicin (RMP), the two most powerful first-line anti-TB drugs
- Extensively Drug-Resistant Tuberculosis: (X-DR-TB) is resistant to Isoniazid (INH) and rifampicin (RMP), plus resistant to any fluoroquinolone and at least one of the three injectable second-line drugs (amicacin, kanamycin, capreomycin)
- Culture Conversion: is said to be achieved if the initially positive culture results were reported negative for M. tuberculosis at any time after multidrug-resistant TB-treatment has started.
- Sputum smear Conversion: is said to be achieved if the initially positive smear results were reported negative for M. tuberculosis at any time after multidrug-resistant TB-treatment has started.
- Early culture conversion: patients whose culture was positive before the initiation of treatment, converts to negative within three months or less after the start of treatment.
- Early sputum smear conversion: patients whose sputum smear was positive before the initiation of treatment, converts to negative within three months or less after the start of treatment.

Data collection

All important data information was collected systematically from all 160 patients treated for MDR-TB using data compilation forms. The dependent variables: the sputum smear conversion and also culture conversion are collected from the bacteriologic laboratory reports. The independent variables: (the personal identifying data or the baseline demographic characteristics) sex, age, weight, the clinical data such as previous treatment of TB, HIV-status, CD4-count, history of diabetes, history of hypertension, the number of anti-TB drugs to which the M. bacterium tuberculosis strain was resistant, the contact history with pulmonary tuberculosis patient, the chest x-ray results, the place of treatment for category I and II were reviewed from the medical records.

On admission for MDR treatment all patients had positive sputum smear and culture results. After the initiation of anti-tuberculosis treatment, sputum smear and also culture conversion was said to be achieved if two consecutive smear and culture results were reported negative for M. tuberculosis. The treatment of patients with multi-drug-resistant TB is on the basis of results of drug susceptibility testing (DST) obtained before the treatment initiation. Each dose is given as directly observed therapy (DOT) throughout the treatment.

Ensuring data quality;

Data enumerator nurses and supervisors (physicians) were selected from St. Peter's TB Specialized hospital working in the MDR-TB ward and were trained for two consecutive days on how data has to be collected. The data enumerators collected all the necessary data from the charts and the supervisors (physicians) working in the MDR-TB ward checked the completeness of the collected data. Finally the principal investigator exhaustively checked all the data collected for their completeness and accuracy before submission for data entry. The charts with incomplete data were excluded.

Data analysis

After the data collection process was completed the collected data was double entered by the Principal Investigator and by a data officer in Armauer Hansen Research Institute (AHRI) using a computer soft ware EPI-info and data was cleaned. The data was exported to SPSS 16.0 and Analysis was performed by these statistical packages and summarized by descriptive statistics and presented with frequency tables. Categorical variables are reported as proportion along with the 95% confidence interval. Continuous variables are reported as mean and median. Internal comparisons were made to compare factors associated with sputum culture conversion and no conversion using Logistic Regression. P-value less than 0.05 were considered statistically significant. (See results on following page)

ETHICAL CONSIDERATION

This research has no harmful effect on patients. There are no invasive procedures involved as the data are collected from charts. All data forms are kept in secure place and the patients' name were not included to maintain confidentiality. The proposal was assessed by the ethical committee at Addis Continental Institute of Public Health jointly with Gondar University and was ethically cleared. In addition the IRB in St. Peter's TB Specialized Hospital and AHRI have also reviewed the proposal. Then the officials in St. Peter's TB specialized hospital were informed about the purpose of the research and permission was obtained to conduct the research.

RESULTS

Socio-demographic Characteristics

Among 160 participants who were treated for MDR-TB at St. Peter's TB-Specialized Hospital since February 2009, 149 (93.13%) participants' charts were included for final analysis. The other 11(6.87%) participants (very recently admitted to hospital) were excluded because the sputum smear conversion results as well as the culture conversion results were missing.

Among the 149(100%) participants who were included in the final analysis, 125(83.90%) were from Addis Ababa and the rest 24(16.10%) were from other Administrative Regions. The age of the participants' ranges from 9 to75 years with a mean age 29.56 and ±SD 10.59 In terms of gender distribution 79(53.00%) of the participants were female and 70(47.00%) were male. (Table.1)

Clinical History

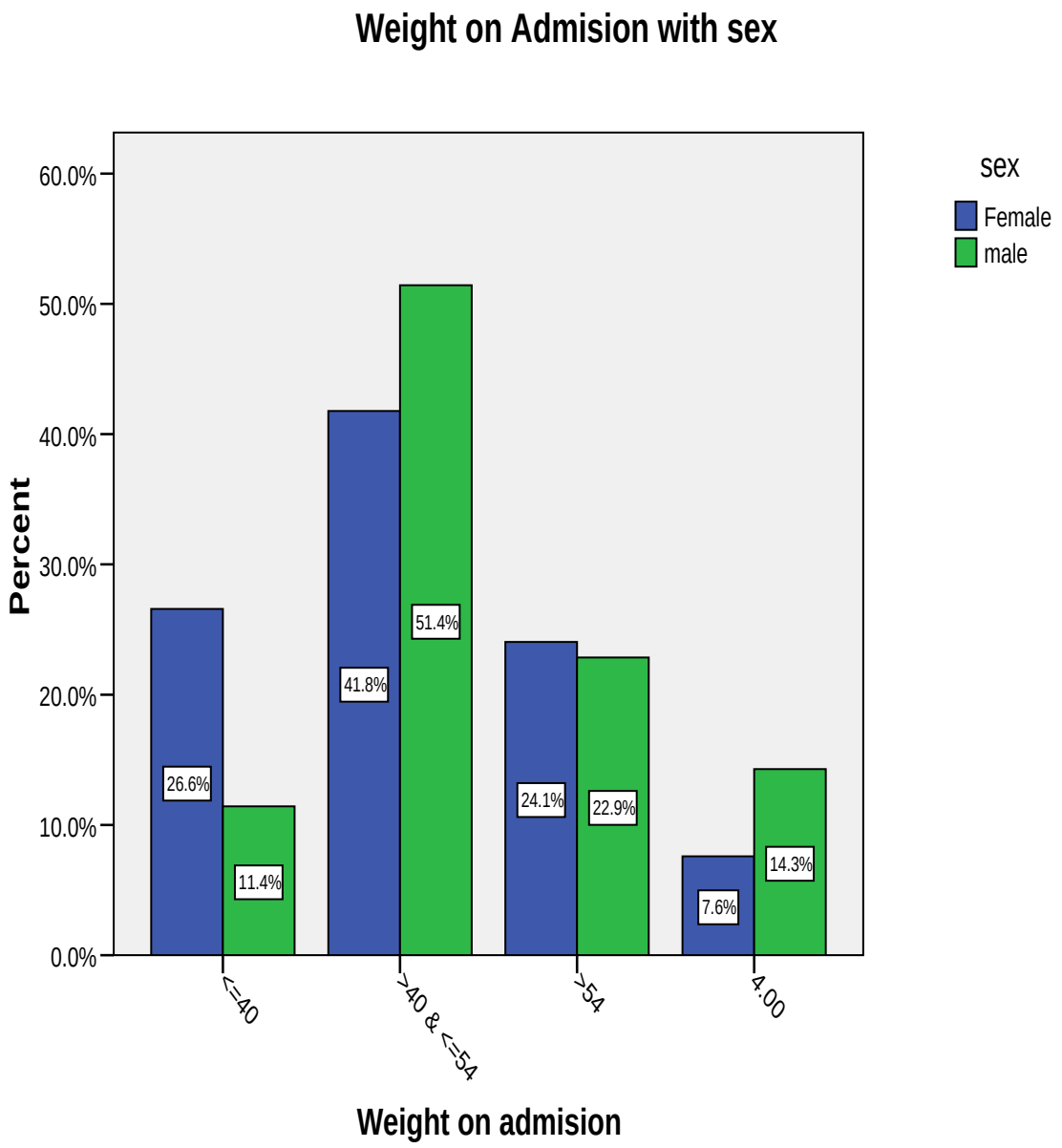
The weight of the participants on admission less than 40 Kg 29(19.50%), 40-50 Kg 69(46.30%), above 50Kg 51(34.23%) (Fig1) Those participants who were previously treated with Category 1 anti-TB treatment are 146(98%) and not treated 3(2.0%). Those participants who were previously treated with Category 2 anti-TB treatment are 145(97.3%) and not treated 4(2.7%). participants having history of contact with pulmonary tuberculosis patient 59(39.6%), with no history of contact with pulmonary tuberculosis patient 90(60.4%). Participants who are HIV positive 36(24.2%), HIV negative 113(75.8%). Participants with CD4-count ≥200 cells/mm3 32(88.89%), with CD4-count ≤ 200 cells/mm3 4(11.11%). (Table1)

Table 1

Socio-demographic and Clinical Characteristics of MDR-TB Patients treated in St. Peter TB-Specialized Hospital Addis Ababa, Ethiopia 2011

Characteristics		No	%
Address			
	Addis Ababa	125	83.89
	Other Administrative Region	24	16.11
Age group			
	Less than24 years	53	35.57
	25-34	58	38.93
	≥35	38	25.5
Sex			
	Female	79	53.02
	Male	70	46.98
Patient Clinical history and Clinical Characteristics			
Previously Treated with Category I Anti-TB			
	Yes	146	97.99
	No	3	2.01
Previously Treated with Category II Anti-TB Rx			
	Yes	145	97.32
	No	4	2.68
Previous History of Contact with PTB-patient			
	Yes	59	39.6
	No	90	60.40
HIV Status			
	Positive	36	24.16
	Negative	113	75.84
CD4 Count done			
	Yes	36	24.16
	Not applicable	113	75.84
CD4 Count			
	≥200 cells/mm3	32	88.89
	<200 cells/mm3	4	11.11
Patient is on treatment for HIV			
	Yes	23	63.89
	No	13	36.11

Fig 1


Weight on Admision with sex
Percent
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
26.6%
11.4%
41.8%
51.4%
24.1%
22.9%
7.6%
14.3%
<=40
>40 & <=54
>54
4.00
Weight on admision
sex
Female
male

Chest X-ray

The Chest X-ray result was available on admission to hospital 149(100%), The Chest X-ray result on admission to hospital revealed with no lung cavity 32(21.48%), With Lung cavity 117(78.52.5%), Chest X-ray which revealed Pulmonary Tuberculosis with pleural effusion 23(15.44%), no pleural effusion 126(84.56%), Chest X-ray result which revealed Pulmonary Tuberculosis without Pneumonia 147(98.7%), not known 2(1.3%). See Table 2

Table 2 Presence of Cavity on Chest X-Ray of MDR-TB Patients treated in St. Peter TB-Specialized Hospital Addis Ababa, Ethiopia 2011

Chest X-ray result	#	%
Chest X-ray result on admission		
Available	149	100
Chest X-ray result on admission revealed		
No Lung Cavity	32	21.48
With Lung Cavity	117	78.52
Chest X-ray on admission Shows P.TB with Pleural Effusion		
Yes	23	15.44
No	126	84.56

Bacteriology

Sputum smear result on admission was positive 144(96.6%), negative 5(3.36%), smear result on the first month after initiation of MDR-TB treatment was positive 42(28.19%), and negative 107 (71.81%). Sputum smear result on the second month after initiation of MDR-TB treatment was positive 16(10.74%), negative 133(89.26%). Sputum smear result on the third month after initiation of MDR-TB treatment was positive 6(4.03%), negative 143(95.97%). Culture result on admission was positive 144(96.64%) and negative 5(3.36%). Culture result on the first month after initiation of MDR-TB treatment was positive 126(84.56%), negative 23(15.44%). The Culture result on the second month after initiation of MDR-TB treatment was positive 76(51.01%), negative 73(48.99. Culture result on the third month after initiation of MDR-TB treatment was positive 26(17.45%), negative 123(82.55%). The culture and sensitivity result on admission was available 149(100%), the culture and sensitivity result on admission revealed resistant to INH and Rifampicin 33(22.15%), resistant to INH, Rifampicin and others 116(77.85%), Sputum smear conversion revealed early conversion (Sputum smear which was positive on admission converts to negative in three or less than three months) 138(92.62%), late conversion(Sputum smear which was positive on admission still remains positive at the end of third month) 11(7.38%). Culture conversion revealed early conversion (Culture which was positive on admission converts to negative in three or less than three months) 118(79.19%), Late conversion (Culture which was positive on admission still remains positive at the end of third month) 31(20.81%), (Table3)

Table 3 Sputum smear and culture Conversion of MDR TB patients on second line treatment at St. Peters Specialized Hospital in Addis Ababa, Ethiopia, June, 2011.

Culture and sputum smear results	**On admission #(%)**	**Month 1 # (%)**	**Month 2 # (%)**	**Month 3 # (%)**
Sputum Smear				
- **Positive**	144(96.6)	42(28.19)	16(10.74)	6(4.03)
- **Negative**	5(3.36)	107(71.81)	133(89.26)	143(95.97)
Culture result				
- **Positive**	144(96.6)	126(84.6)	76(51.01)	26(17.45)
- **Negative**	5(3.36)	23(15.44)	73(48.99)	123(82.55)

Table4

Adjusted Factors associated with culture conversion in MDR TB patients on second line anti-TB treatment St. Peter TB-Specialized, Addis Ababa, June 2011

	Culture early converter	Culture Non-converters	COR(95% C	AOR (95% CI)
Sex				
Female	65(82.3%)	14(17.7%)	1.0	
Male	58(82.9%)	12(17.1%)	0.96(.41-2.24)	0.77(0.28-2.13)
Age group				
≤24 years	48(90.6%)	5(9.4%)	3.43(1.06-11.05)	0.79(.23-2.75)
25-34-	47(81.01%)	11(19.0%)	1.53(.58-4.05)	0.93(.24-3.86)
≥35-	28(73.7%)	10(26.3%)	1.0	
Weight at admission				
≤40 Kg	25(86.2%)	4(13.8%)	0.58(.17-1.91)	
40-50Kg	54(78.3%)	15(21.7%)	1.01(0.27-3.78)	
>50Kg	44(86.3%)	7(13.7%)	1.0	
HIV status				
-Positive	104(92.0%)	9(8.0%)	10.34(4.02-26.59)	0.90(0.03-0.29)
-negative	19(52.8%)	17(47.2%)	1.0	
pleural effusion				
- Present				
-absent	16(69.6%)	7(30.4%)	0.41(0.15-1.12)	1.82(.56-5.92)
	107(84.9%)	19(52.8)	1.0	
History of Rx with Cat II				
Rx	3(75.0%)	1(25.0%)	1.0	
-Yes	120(82.8%)	25(17.2%)	0.63(0.06-6.26)	
-No				
Contact with TB case				
-Yes				
-No	72(80.0%)	18(20.0%)	1.0	
	51(86.4%)	8(13.6%)	0.62(.25-1.55)	1.79(0.64-5.04)

Taking the early convertors as reference; the Culture conversion in the third month for HIV positives, revealed 104(92.0%) with OR 10.34(4.02-26.59).This is very significant and it shows that HIV-positives are converting ten times slower than the HIV negatives; that is HIV negatives are early convertors.

The culture conversion in the third month for age group ≤ 24 years revealed 48(90.6%) with OR3.43 (1.06-11.05) and P .039. This is also significant and it indicates that the young (age≤ 24) are the early convertors.

DISCUSSION

Almost 95% sputum smear converted and 82% culture converted on the third month of MDR treatment Therefore, the majority of our patients can be considered early converters to the treatment which has significant implication to the TB program in terms of further prevention of spread of MDR TB cases and prevention of XDR TB. It indicates that patients did not have exposure to the second lines drugs. It also has an implication in terms of the bed occupancy rate; however, this has to be given serious consideration since this high rate of conversion wouldn't have been achieved had it not been for strict observed treatment in admitted patients. When we compare ours with the retrospective study done in Latvia in 2000; ours is very good and encouraging in terms of treatment response.

The early converters are the young [OR3.43 (1.06-11.05) and P .039] and the HIV positives are the late convertors [104(92.0%) with OR 10.34(4.02-26.59)]. This may be due to their immunological status, as the young and those without HIV have better immunological status which can synergize the effect of the treatment. Those who are HIV-positive are the late convertors and our study has similar results when compared with the retrospective cohort study of patients in HIV-prevalence settings in the Lesotho national MDR-TB program.

As St Peter TB-Specialized Hospital is the only MDR-TB treatment center for the whole country (recently the Gondar MDR-treating center is added), currently only few patients could get the chance to treatment and the remaining majority is still outside spreading the diseases, therefore, it is good to know who the early converters are. If there is a decision to plan for outpatient observed treatment it can focus on the young and the HIV negatives.

Among the 149(100%) participants who were included in the final analysis 125(83.9%) were residents Addis Ababa and the rest were from other Administrative Regions. This could be because they have access to the treatment centre and one cannot conclude the number of MDR cases is higher in Addis Ababa than in regions. Nevertheless, it is important to note that a large number of MDR TB cases are living in this city which is very alarming to the TB control program as the city is densely populated and is a place for many international offices. It also calls to assess the situation in the rest of the regions.

The sputum smear conversion in the first month after the start of anti-TB treatment for MDR-TB is 107 (71.81%). This is very high and different than what we observe in other literatures. This also need further study to identify what other possible reasons exist. Even though the culture conversion rate is not as high as the sputum smear conversion; we can see that the culture conversion at the end of third month is 123(82.55%). This is also very high result when compared with other literatures. This would also indicate that the patients did not have exposure to the second lines drugs.

Strength of the study

- This study is the first systematic evaluation since the start of MDR-TB treatment in the country
- Data was collected by the Nurses who are assigned in the MDR-TB ward who knows very well the documentation and archiving system of the hospital and this ensures the data quality
- After the data was collected by the data enumerator nurses data verification was carried out by the supervisors (physicians) working in the MDR-TB ward and final verification was done by the Principal Investigator; all these also ensures the data quality additionally.

Limitations of the Study

- We rely only on the available information. According to literatures diseases like Diabetes and Hypertension are very important factors for the delay of sputum smear and also culture conversion. These important factors were not documented in the patients' chart. Therefore, we were not able to do analysis and report if these diseases were also factors for delay of conversion in our study.
- History of previous treatment; Place of treatment (Hospital, H/center, Private Clinic etc…) was not documented in patient's chart and we were not able to identify in which place was MDR-TB significant.
- Defaulters are prone to develop drug resistance. In this study the history of treatment default was also not documented in the patients' chart; so we were not able to comment if history of default has contributed to the development of Drug Resistant-TB.

Conclusion

- Sputum early convertors are 92.62% and Culture early convertors are 79.19%.These reveal good treatment response and could predict high cure rate.
- The Study confirmed that > 92% of MDR patients convert their culture in ≤ 3/12:

  - This could minimize the hospital stay of the patients which currently extend up to 6/12;
  - It would increase the turn-over;
  - This in-turn would increase the number of patients to be treated
  - And finally minimize MDR-TB load of the country
- As St Peter TB-Specialized Hospital is the only MDR-TB treatment center for the whole country, (recently the Gondar MDR-treating center is added), currently only few patients could get the chance to treatment and the remaining majority is still outside spreading the disease, therefore, it is important knowing who the early converters are in order to utilize efficiently the limited hospital service.
- If there is a decision to plan for outpatient observed treatment we can consider/ focus on :

  -The young and

  - The HIV negatives

RECOMMENDATIONS

For Policy makers:

- Ambulatory DOTS can be considered for MDR patients after 3 months of optimal stay in the hospital.
- Encourage referrals from other administrative regions for MDR-TB Rx.
- Give Special attention to the elderly and HIV-positives

For program managers and health facility implementers:

- Important to improve the recording of patients' information as it is needed to evaluate the treatment program

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ANNEX I

DATA COMPILATION FORM

DATA SOURCE: Patient's Medical record

(I) Patient's Card number /……/……/……/……/……/……/……/

(II) Patient's Cod number /……/……/……/

(III) Date of Admission day/……/……/month/……/……/year/……/……/……/……/

(IV) Address. (1) Addis Ababa (2) Other administrative region /……/

(V) Age……. /……/……/ Years

(VI) Sex…….. (1) Female (2) Male……/……/

(VII) Weight on Admission for MDR-TB treatment ……. /……/……/ Kg

(VIII) Weight after two months of MDR-TB treatment ……. /……/……/ Kg

(IX) Sputum Smear result on admission for MDR-TB treatment

(1) Positive (2) negative (3) Contaminated (4) not available /……/

(X) Sputum Smear result at first month after MDR-TB treatment

(1) Positive (2) negative (3) Contaminated (4) not available /……/

(XI) Sputum Smear result at second month after MDR-TB treatment

(1) Positive (2) negative (3) Contaminated (4) not available /……/

(XII) Sputum Smear result at third month after MDR-TB treatment

(1) Positive (2) negative (3) Contaminated (4) not available /……/

(XIII) A. Culture result on admission for MDR-TB treatment

(1) Positive (2) negative (3) contaminated (4) not available /……/

(XIV) Culture result at first month after MDR-TB treatment
(1) positive (2) negative (3) Contaminated (4) not available /……/

(XV) Culture result at second month after MDR-TB treatment
(1) positive (2) negative (3) Contaminated (4) not available…… /……/

(XVI) Culture result at third month after MDR-TB treatment
(1) positive (2) negative (3) Contaminated (4) not available……..…../……/

(XVII) Culture and sensitivity result on admission for MDR-TB treatment
(1) available (2) not available……./……/

(XVIII) Culture and sensitivity result on admission for MDR-TB is resistant to
(1) INH (2) RIF (3) INH & RIF (4) INH & RIF Plus others…..……/……/

(XIX) Previously treated with Category-I anti-TB drugs

(1) Yes (2) no (3) Not known…….……../……/

(XX) Previously treated with Category-II anti-TB

(1) Yes (2) no (3) not known……./……/

(XXI) Place for CAT- I of Anti-TB treatment

(1) Health center (2) Hospital (3) Not known…….…….../……/

(XXII) Place for CAT- II of Anti-TB treatment

(1) Health center (2) Hospital (4) Not known…….……../……/

(XXIII) Patient has defaulted his treatment while he/she was on CAT- I of Anti-TB treatment

(1) Yes (2) No (3) Not known …..…….. /……/

(XXIV) Patient has defaulted his treatment while he/she was on CAT-II of Anti-TB treatment
(1) Yes (2) No (3) Not known…….…….…/……/

(XXV) Has previous History of contact with Pulmonary TB patient

(1) Yes (2) No (3) Not known…….……/……/

(XXVI) Chest X-ray result on admission for MDR TB treatment

(1) Available (2) not available……./……/

(XXVII) Chest X-ray revealed (1) No lung cavity (2) Left lung cavity (3) Right lung cavity
(4) bilateral lung cavities (5) not applicable……...……/……/

(XXVIII) Chest X-ray revealed P.TB with pleural effusion

(1) Yes (2) No (3) not applicable……..……../……/

(XXIX) Chest X-ray revealed P.TB with Pneumonia (1) Yes (2) No (3) not applicable…/……/

(XXX) Patient is Diabetic..... (1) Yes (2) no (3) not known……/……/

(XXXI) Patient is on treatment for Diabetes.....

(1) Yes (2) no (3) not applicable…….……/……/

(XXXII) Patient is Hypertensive …. (1) Yes (2) no (3) not known..…..…..……/……/

(XXXIII) Patient is on treatment for hypertension

(1) Yes (2) no (3) not applicable……../……/

(XXXIV) HIV status…….. (1) Positive (2) Negative (3) Not tested……/……/

(XXXV) CD4-count done (1) Yes (2) no (3) not applicable……./……/

(XXXVI) CD4-count is …….

(1) ≥ 200 cells/mm3 (2) < 200 cells/mm3 (3) not applicable……./……/

(XXXVII) Patient is on treatment for HIV……..

(1) Yes (2) no (3) not applicable…..……. /……/

(XXXVIII) Patient was on treatment for any other disease other than Diabetes, Hypertension or HIV…… (1) Yes (2) No (3) Not known……../……/

Completed by: Name ……

Signature: …… Day/……/……/month/……/……/year/……/……/……/……/

Checked by: Name……
Signature: ……
Day/……/……/month/……/……/year/……/……/……/……/

Verified by: Name……..
Signature……
Day/……/……/month/……/……/year/……/……/……/……/

ANNEX II

CONSENT FORM

Since this research is a retrospective study, we do not have any contact with the patients. The base-line demographic characteristics and all important information are collected from the available medical records; treatment charts; bacteriologic laboratory records and chest x-ray results. Therefore, we do not have the need for consent papers.

DECLARATION

I the undersigned, declare that this thesis is my original work, has not been presented for a degree in this or on another university and that all source materials used for this thesis have been fully acknowledged.

Name: Tesfamariam Mebrahtu (Dr.)

Signature_____

Date of submission: _____

This thesis paper work has been submitted with my approval as university advisor

Name_____

Signature_____

Date: _____

Joint MPH Program

University of Gondar and Addis Continental Institute of Public Health

Title: Determinant Factors and time to Smear and Culture conversion among Multi-drug Resistant Tuberculosis Patients in St. Peter Tuberculosis Specialized Hospital Addis Ababa

By

Tesfamariam Mebrahtu Ukube

Addis Continental Institute of Public Health and School of Public Health, University of Gondar

Approved by the Examining Board

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Chairman, Dep. Graduate Committee

_____ _____

Advisor

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Examiner

_____ _____

Examiner